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(54) Title: A NASAL SPRAY CONTAINING AN INTRANASAL STEROID AND AN ANTIHISTAMINE

(57) Abstract

The present invention relates to pharmaceutical compositions for nasal administration comprising: a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof; b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, rocastine, tripelennamine, meclizine, tripolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof; and c) an aqueous, intranasal carrier wherein the composition is free of capsaicin and, preferably, free of powders or granules. The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention.

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A NASAL SPRAY CONTAINING AN INTRANASAL STEROID AND AN ANTIHISTAMINE

TECHNICAL FIELD

The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine.

BACKGROUND OF THE INVENTION

Allergic disorders remain a leading cause of both acute and chronic illnesses the world over. These illnesses are often times present in the form of acute or chronic rhinitis. The symptoms of allergic rhinitis are nasal, ocular and palatial irritation, sneezing and hypersecretion. These symptoms occur following exposure to allergens. The main allergens are usually grass and/or tree pollens, hence, allergic rhinitis is common during the spring and summer months.

The symptoms of allergic rhinitis are believed to be due to the stimulation of H-1 receptors by histamine, followed by reflexive activation of parasympathetic nerves causing increases in nasal secretion and obstruction. Histamine is initially released from the tissue mast cells upon sensitization of the mast cells. This sensitization results when airborne allergens combine with specific IgE antibodies attached to mast cell membranes.

Antihistamines and/or decongestants have traditionally been the drugs of choice in treating allergic rhinitis. Other forms of therapy include the use of cromolyn sodium, hypertonic salt solutions or immunotherapy.

Hagen et al., U.S. Patent 4,767,612, discloses nasal corticosteroid therapy as an effective means of treating allergic rhinitis; and is herein incorporated by reference. The effectiveness of these compounds is limited, however, by the slow onset of action characteristic of nasal corticosteroids (activity generally occurring anywhere from 1-3 days) and, occasionally, the occurrence of "break-through" symptoms. For similar reasons, such products also tend to limit consumer compliance.

Notwithstanding the many disclosures in the area of allergic rhinitis, there is still a need for additional formulations free of irritating powders or granules as well as irritating drugs such as capsaicin which provide fast and improved symptomatic relief with increased user acceptance and compliance.

The present inventor has found that by combining a nasal corticosteroid with a fast acting antihistamine, not only is the delay in onset considerably decreased, but the resulting compositions of the present invention also provide improved relief of those symptoms generally associated with either seasonal or perennial allergic rhinitis.

Additionally, combining the antihistamine with the nasal steroid results in improved symptom relief (e.g., improved nasal and ocular symptom relief). Furthermore, intranasal administration of antihistamines requires dosage amounts less than those associated with oral administration, thereby reducing potentially annoying side effects (e.g., drowsiness). By addressing such problems, the compositions of the present invention also help in improving overall patient compliance.

It is, therefore, an object of the present invention to provide pharmaceutical compositions having improved effectiveness in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinitis.

Another object of the present invention is to provide an irritant free pharmaceutical composition for use in the treatment of symptoms generally associated with either seasonal or perennial allergic rhinitis.

A further object of the present invention is to provide a safe and effective method for treating seasonal or perennial allergic rhinitis.

These objects and other objects will become more apparent from the detailed description that follows.

SUMMARY OF THE INVENTION

The present invention relates to pharmaceutical compositions for nasal administration comprising:

a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;

b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, rocastine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine pharmaceutically acceptable salts thereof and mixtures thereof; and

c.) an aqueous, intranasal carrier

wherein the composition is free of capsaicin and, preferably, free of powders or granules.

The present invention also relates to a method for the treatment of symptoms associated with seasonal or perennial allergic rhinitis comprising the administration of a safe and effective amount of the intranasal pharmaceutical compositions of the present invention.

By "symptoms associated with seasonal or perennial allergic rhinitis" is meant ocular and palatial irritation, sneezing, mucoid hypersecretion, nasal congestion and itching.

By "safe and effective amount," as used herein, is an amount that is effective to mitigate and/or treat the symptoms for which the active ingredient is indicated in a human without undue adverse side effects commensurate with a reasonable risk/benefit ratio.

By "fast acting," as used herein, refers to an onset of action which occurs within 15-30 minutes after administration.

The pH of the compositions is preferably from about 5 to about 9, more preferably from about 5.5 to about 7.

All percentages and ratios herein are by weight unless otherwise specified. Additionally, all measurements are made at 25°C unless otherwise specified.

DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention contain the essential components as well as various optional components as indicated below.

More specifically, the compositions of the present invention are for nasal administration and contain a therapeutically safe and effective amount of the pharmaceutical agents described herein. They are preferably provided as isotonic aqueous solutions, suspensions or viscous compositions which may be buffered to a selected pH.

Essential Ingredients

Glucocorticoid Agents

Agents within this class have potent glucocorticoid activity and weak mineralocorticoid activity. Glucocorticoid agents most useful to the present invention include those selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof.

When used in the compositions of the present invention, the glucocorticoid component is preferably present at a concentration of from about 0.001% to about 0.1%, more preferably from about 0.01% to about 0.1%.

Antihistaminic Agents

Antihistamines most useful to the present invention are histamine H-1 receptor antagonists which are fast acting. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: alkylamines, ethanolamines, ethylenediamines, piperazines, phenothiazines, piperidines.

Examples of useful fast acting antihistamines include acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, rocastine, phenindamine or pharmaceutically acceptable salts and mixtures thereof. Without being limited by theory, it is believed that the antihistamine additionally improves the delivery of the glucocorticoid, improving the glucocorticoid's onset of action. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 3.0%, more preferably from about 0.01% to about 1%.

Pharmaceutically-Acceptable Aqueous Nasal Carrier.

One other essential component of the present invention is a pharmaceutically-acceptable intranasal carrier. Preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid. The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, citric acid, sodium tartrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium choride equivalents are disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990), which is herein incorporated by reference.

Most preferred for use herein are aqueous, isotonic saline solution carriers. These solutions which generally contain sodium chloride as the salt are fully described in Remington's Pharmaceutical Sciences, 17th edition (1985) p. 835, which is herein incorporated by reference. The salt is present in the solution at a level of about 0.01% to about 2%, preferably from about 0.5% to about 1.0% and most preferably from about 0.5% to about 0.75%.

The combination of any of the above described antihistamines and glucocorticoids can be conveniently administered nasally to warm-blooded animals to elicit the desired therapeutic response by formulating it into a nasal dosage form, together with a nontoxic pharmaceutically-acceptable nasal carrier. Suitable nontoxic pharmaceutically-acceptable nasal carriers are known to those skilled in the art and are also fully disclosed in Remington's Pharmaceutical Sciences, 17th edition, 1985. Obviously, the choice of suitable carrier forms will depend on the exact nature of the particular nasal dosage form required, e.g., whether the drug is to be formulated into a nasal solution (for use as drops or as a spray), a nasal suspension, a nasal ointment, a nasal gel or another nasal form.

Preferred nasal dosage forms are solutions, suspensions and gels, which normally contain sodium chloride in a major amount of water (preferable purified water) in addition to the antihistamine and glucocorticoid. Minor amounts of other ingredients such as pH adjusters (e.g., a base such as NaOH), emulsifiers or dispersing agents, buffering agents, preservatives, wetting agents and jelling agents (e.g., methylcellulose) may also be present.

Preferably the composition is applied to the nasal mucosa via topical application of a safe and effective amount of the composition to treat nasal symptoms. The amount of the antihistamine and glucocorticoid combination and frequency of topical application to the nasal mucosa may vary, depending upon personal needs, but it is suggested, as an example, that topical application range from about once per day to about three times daily, preferably twice daily, most preferably once daily. As a practical matter the selected therapeutic compositions will normally be prepared in unit dosage forms or actuations to contain therapeutically effective amounts of the selected antihistamine and glucocorticoid combination. In specific instances fractions of these dosage units or multiple dosage units will be employed. Typically dosage units may be prepared to deliver from about 0.5 mcg to about 50 mcg of the glucocorticoid agent and from about 5 mg to about 75 mg of the antihistaminic agent per dose (e.g., 50 mg to about 150 mg of the spray composition). A typical dose contains one to three sprays per nostril.

Optional Ingredients

An additional antihistamine may be optionally incorporated into the compositions of the present invention. Such antihistamines would preferably include those having a durations of action greater than 6 hours. Examples of such antihistamines include terfenadine, azelastine, cetirizine, astemizole, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof. Active metabolites of the above antihistamines may also be used. Examples of such metabolites are disclosed in U.S. Patents 3,878,217 and 4,254,129, issued April 15, 1975 and March 3, 1981, respectively, to Carr et al.; U.S. Patent 5,375,693, issued December 27, 1994, to Woosley et al.; and European Patent 648759, each of which are herein incorporated by reference in their entirety.

Optional ingredients useful in the present invention include decongestants. Decongestants useful to the present invention may be selected from among the class of sympathomimetic agents; examples of which include pseudoephedrine, desoxyephedrine, propylhexedrine, phenylpropanolamine, xylometazoline, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline and pharmaceutically acceptable salts thereof.

Also useful as decongestants are the 5-(2-imidazolinylamino)benzimedazole compounds. Mixtures of these decongestants can also be used.

When used in the compositions of the present invention, the sympathomimetic agents may be incorporated at concentrations, preferably, of from about 0.01% to about 0.5%, more preferably from about 0.05% to about 0.1%.

The compositions of the present invention may also contain a xanthine derivative such as caffeine and methylxanthine and the like. The xanthine derivative may preferably be incorporated at concentrations of from about 0.01% to about 1%, most preferably from about 0.1% to about 0.5. Mixtures of xanthine derivatives may also be incorporated.

The compositions of the present invention may also contain antiallergics. Suitable antiallergics include, but are not limited to, cromolyn, ketotifen, N-allyl-(dichloro-3, 4-benzyl)-2-methylamino-2-propanol-1, AP-582 (Pharmaprojects No. 3055-under investigation by Ariad Pharmaceuticals), Andolast, oxatamide and pharmaceutically-acceptable salts thereof. Mixtures of these antiallergics may also be used.

Similarly, mucolytics such as acetylcysteine and anticholinergics such as ipratropium bromide may also be used in the compositions of the present invention.

Also of optional use in the compositions of the present invention are nonopiate analgesics such as oxaprozin. The intranasal use of oxaprozin is described in Namiki et al., Studies on improvement of pharmaceutical preparations prescribed in hospitals. VI. oxaprozin nasal spray, Drug Design and Delivery 1988;2:pp. 311-321, herein incorporated by reference. Further examples of preferred nonopiate analgesics include, but are not limited to, acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenbuprofen, fenoprofen, ketorolac, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically-acceptable salts thereof, optically active racemates thereof and mixtures thereof. Preferred for use herein are the S(+) isomers of the nonopiate analgesics. Still further examples of such drugs are disclosed in U.S. Patent No. 4,522,828, to Sunshine et al., issued June 11, 1985; this patent being incorporated herein by reference in its entirety.

Synthetic opiate analgesics such as butorphanol may also be incorporated into the compositions of the present invention. The intranasal use of butorphanol is described in Baumel, Migraine: A pharmacologic review with newer options and delivery modalities, Neurology 1994;44(supp):pp. s13-s17, herein incorporated by reference. Further examples of preferred synthetic opioid analgesics include alfentanil, buprenorphine, fentanyl, meperidine, methadone, nalbuphine, natrexone, propoxyphene, pentazocine, sufenanil, pharmaceutically-acceptable salts thereof and mixtures thereof.

Leukotriene receptor antagonists may also be incorporated into the compositions of the present invention. Suitable examples include, but are not limited to, experimental

agents such as Zafirlukast (Accolate, Zeneca), MK-571 (Merck, Sharp and Dohme), LY171883, Wy-45,911, LY163443, ONO-RS-411 and ONO-RS-347 and ICI 198,615. A more detailed discussion of leukotriene receptor antagonists is found in European Patent Application 318093, and Fleisch, J. H., Development of Cysteinyl Leukotriene Receptor Antagonists, Vol. 12 Advances in Inflammation Research 173-189 (A. Lewis et al. ed. 1988), Both of which are herein incorporated by reference in their entirety.

Lipoxygenase inhibiting compounds may also be incorporated into the compositions of the present invention. Suitable examples are discussed in U.S. Patent 4,873,259, to Summers et al., issued October 10 1989 and U.S. Patent 5,037,853, to Brooks et al., issued August 6, 1991, both of which are herein incorporated by reference in their entirety.

Various aromatic components (e.g., aldehydes and esters) may also be used. These aromatics include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); and 2-dodecenal (citrus, mandarin). Additional aromatic components suitable for use in the present invention include those described in U.S. Patent 4,136,163 to Watson et al., U.S. Patent 4,459,425 to Amano et al., and U.S. Patent 4,230,688 to Rowsell et al.; all of which are herein incorporated by reference. Mixtures of these aromatics can also be used.

Viscosity of the compositions may be maintained at the selected level using a pharmaceutically-acceptable thickening agent. Methyl cellulose is preferred because it is readily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, microcrystalline cellulose, carboxymethyl cellulose, chitosan, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutical salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Preferred compositions within the scope of this invention will contain from about 0.01% to about 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any f a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with the selected

agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

Enhanced absorption across the nasal membrane can be accomplished employing a therapeutically acceptable surfactant. Typical useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Polysorbate 80, Polyoxyl 40 Stearate, Polyoxylethylene 50 Stearate and Octoxynol, as well as Oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as tyloxapol) or mixtures thereof. The usual concentration is from 0.5% to 10% based on the total weight.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. Benzyl alcohol is suitable, although a variety of preservatives including, for example, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, phenylmecuric acetate or benzalkonium chloride may also be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected Mixtures of these preservatives may also be used.

Combinations of any of the above optional components may also be incorporated.

Other Optional Components. A variety of additional ingredients may be added to the emulsion compositions of the present invention. These additional ingredients include various polymers for aiding the film-forming properties and substantivity of the formulation, preservatives for maintaining the antimicrobial integrity of the compositions, antioxidants, and agents suitable for aesthetic purposes such as fragrances, pigments, and colorings.

The compositions can also contain low levels of insoluble ingredients added, for example for visual effect purposes, e.g. thermochromic liquid crystalline materials such as the microencapsulated cholesteryl esters and chiral nematic (nonsterol) based chemicals such as the (2-methylbutyl) phenyl 4-alkyl(oxy)benzoates available from Hallcrest, Glenview, Illinois 60025, U.S.A., Mixtures of these and the above ingredient may also be used.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many

variations thereof are possible without departing from the spirit and scope of the invention.

Example I

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described below.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
chlorpheniramine	0.500
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.050
benzalkonium chloride	0.020
phenylethyl alcohol	0.025
distilled water	q.s. 100ml

[1]microcrystalline cellulose and sodium carboxymethyl cellulose, supplied FMC Corporation.

In an appropriately sized vessel, the above listed ingredients are added one at a time to water with mixing, allowing each to dissolve before adding the next. After all the ingredients have been added, purified water is used to bring the batch to the appropriate weight.

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example II

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
flunisolide	0.025
chlorpheniramine	0.350
levocabastine	0.0125
propylene glycol	2.000
polyethylene glycol	1.000
ethylenediamine tetraacetic acid	0.050

benzalkonium chloride	0.010
distilled water	q.s. 100ml

The above ingredients are combined

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
acrivastine HCl	0.100
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. 100ml

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms.

Example IV

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
beclomethasone diproprionate, monohydrate	0.042
chlorpheniramine	0.500
oxymetazoline	0.050
avicel RC - 591[1]	1.200
dextrose	5.100
polysorbate 80	0.050
benzalkonium chloride	0.020
phenylethyl alcohol	0.025
distilled water	q.s. 100ml

[1]microcrystalline cellulose and sodium carboxymethyl cellulose, supplied FMC corporation.

Administration of approximately 0.5 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof or by using, in whole or in part, equivalent amounts of other fast acting antihistamines such as carbinoxamine, diphenhydramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, rocastine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a sympathomimetic amine such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolinylamino)benzimedazoles, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.

What is claimed is:

1. A pharmaceutical composition comprising:
   a) a safe and effective amount of a glucocorticoid selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof;
   b) a safe and effective amount of a fast acting antihistamine selected from the group consisting of acrivastine, carbinoxamine, diphenhydramine, chloropheniramine, brompheniramine, dexchloropheniramine, doxylamine, clemastine, promethazine, rocastine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripelennamine, meclizine, triprolidine, azatadine, cyproheptadine, phenindamine, pharmaceutically acceptable salts thereof and mixtures thereof; and
   c) an aqueous, intranasal carrier

   wherein the composition is free of capsaicin.

2. A composition according to Claim 1 in the form of an isotonic aqueous solution.

3. A composition according to Claim 1 or 2 wherein the glucocorticoid is beclomethasone.

4. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a sympathomimetic amine selected from the group consisting of pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, pharmaceutically acceptable salts thereof and mixtures thereof.

5. A pharmaceutical compositions according to any one of the preceding Claims, which further comprises an additional antihistamine selected from the group consisting of terfenadine, azelastine, cetirizine, astemizole, ebastine, ketotifen, lodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof.

6. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a non-steroidal anti inflammatory agent.

7. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a lipoxygenase inhibitor or antagonist.

8. A pharmaceutical composition according to any one of the preceding Claims, which further comprises a nonopiate analgesic.

9. A method for treatment of seasonal allergic rhinitis or using a safe and effective amount of the composition of any one of the preceding Claims.

10. A method for treatment of perennial allergic rhinitis using a safe and effective amount of the composition of any one of the preceding Claims.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/09518

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/57 A61K31/56 A61K31/44 A61K31/445 A61K31/415
//(A61K31/57,31:44),(A61K31/57,31:44,31:445),(A61K31/57,31:44,
31:415)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 01337 A (MCNEIL PPC INC) 16 January 1997 * see the whole application * ---	1-3
Y	INT. J. PEDIAT. OTORHINOLARYN., vol. 3, no. 4, 1981, pages 287-294, XP002040649 BUSINCO ET AL.: "Clinical and therapeutic aspects of sinusitis in children with bronchial asthma" * see summary, Table VII * --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1997	24.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (- 31-70) 340-2040, Tx. 31 651 epo nl, Fax (- 31-70) 340-3016	Isert, B

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/09518

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. ALLERG. CLIN. IMMUNOL., vol. 79, no. 6, 1987, pages 887-892, XP002040650 VANZIELEGHEM ET AL. : "A comparison of budesonide and beclomethasone dipropionate nasal aerosols in ragweed-induced rhinitis" * see the abstract, Fig. 4 *	1-4
Y	ALLERGY ASTHMA PROC, vol. 17, no. 3, 1996, pages 149-156, XP002040651 RATNER ET AL.: "New formulation of aqueous flunisolide nasal spray in the treatment of allergic rhinitis: comparative assessment of safety, tolerability, and efficacy" *see the abstract *	1-4
P,Y	WO 97 01341 A (MCNEIL PPC INC) 16 January 1997 * see claim 1 *	1-3
E	EP 0 780 127 A (PROCTER & GAMBLE) 25 June 1997 * see claim 1; page 3, lines 24-30 *	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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